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EDITORIAL

REFLECTIONS ON PRESENT TIMES

We live in a world which is sorely troubled and the word crisis hits the headlines. During the last decade our people have lived at great tension; crisis has followed crisis with such regularity that the very word has become trite. After six years of war and all its anxiety and full-blooded effort, it was natural that we should expect a period of respite and relaxation. Yet, after two years of peace, we find that, although the threat of physical violence is abated, we are threatened with something equally as evil, i.e., starvation. Is this state of affairs due to the failure of nature or is it of man's making? Mother Nature rarely fails to meet her obligations; if she does, that failure is always regional and is compensated by fruitfulness in other parts.

In ancient times, owing to lack of scientific knowledge and poor communications, local famine and pestilence were common incidents and caused great suffering. In modern times, there is no excuse for such things. Undoubtedly, therefore, the present crisis is of man's making, or a better expression would be to attribute it to his failure to apply his knowledge and resources and to make use of the products of a beneficent nature to the full.

It would appear that we are prepared to devote more time and energy to the ways and means of destruction than to those which create. In the world of to-day there are regions of plenty, and if surplus products could be transferred to parts where there is want or scarcity all might be well. In many places production falls far short of capacity. Many areas which could be almost self-sufficient are content to depend on others.

The remedies for our present plight can be classified under three heads: production, transport and finance, using the latter term in its true sense, meaning the tokens of exchange.

Finance and transport are interdependent upon political strategy, and so it is not the province of a professional journal to make comment. The question of production is an entirely different matter, and the production of food products certainly concerns deeply the veterinary surgeon; indeed, he is an essential factor.

High production means good husbandry, both of animal and plant. Although primarily interested in animal husbandry, the veterinary surgeon's interests have

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a wide range and include soil, plant, animal and man. Animals convert the products of the soil into human food. Man's existence is dependent upon his animals, they depend upon the plants, which in turn depend upon the soil. Also, animals play no small part in preserving and enhancing the fertility of the soil.

In production, therefore, there is a balanced cycle—failure in any one of its parts upsets the whole. Good animal husbandry is an essential factor in the recovery from our present plight, and it is in this realm that the veterinary surgeon can play a full part. Good animal husbandry is dependent upon scientific breeding and selection, good nutrition, and the control and prevention of disease. To increase production, one must increase numbers, and as a rule an increase in numbers means greater liability to disease. Good nutrition and pasture management are essential if the animals are to be kept in good health. It is proposed to increase the quantities of imported foods and also the farmer will be allowed to use a percentage of his own grown cereals for animal food. In spite of this, it is difficult to visualise how any great increase in numbers can be effected unless some system of "Ley" farming is adopted. This is a change in method which must be watched with great care. There is already some evidence that "Ley" farming brings new problems to the veterinary surgeon, and we should be constantly on guard.

It will be seen that the veterinary surgeon has a great part to play in the present emergency. In the past the cure and prevention of disease *per se* has absorbed his attention; in the future he has to widen his scope and become the farmer's advisor in all the problems of animal husbandry, from birth to maturity, for good breeding, nutrition and management are the great enemies of disease, and animals kept under such conditions are more prolific and come to maturity at an earlier date than do those which are kept under less salubrious conditions.

In the meantime, our efforts to cure, control and prevent disease should be redoubled, for it will be many years before the full effects of good animal husbandry in the elimination of disease can bear fruit.

GENERAL ARTICLES

A STUDY OF ISOLATION IN FOWL PARALYSIS (LYMPHOMATOSIS)

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FROM recent studies (Asplin [1944], Glover [1940]) it seems certain that fowl paralysis is caused by a filterable virus. In continuation of previous work (Johnston and Wilson, 1937, 1939) the experiments reported in this paper, which were completed in 1939, were designed to investigate the mode of spread of the disease in birds under conditions of even more strict isolation than before. The results suggest that isolation can restrict the extent of an outbreak but that transmission can result, probably through the egg, from apparently healthy parents to birds hatched and reared in isolation.

Two essentials for research in this subject are a stock free from fowl paralysis and strict isolation of that stock. At the time our work began no fowl-paralysis-free stock was available. But complete isolation of large groups was feasible, and this appeared to be a useful line of investigation which could be followed up profitably even in the absence of a free stock. Further, it was possible that a fowl-paralysis-free stock might be obtained in this way, but should this not materialise there would be additional evidence that the disease is transmitted from parent to offspring *via* the egg.

From Johnston and Wilson's (1937, 1939) experiments two facts were evident: that even partial isolation reduced the incidence of the disease and that isolation either increased the period of incubation or delayed primary infection. Moreover, the reduction in incidence of the disease among the isolated birds had been considerable: 4.70 per cent. among isolated White Leghorns and 0.76 per cent. among isolated Brown Leghorns compared with 10.87 per cent. and 3.37 per cent. respectively in the non-isolated controls.

Methods

In order to appreciate the full significance of our present objective and the methods about to be described, the reader is referred to the communications previously published (Johnston and Wilson, 1937, 1939).

Equipment.—A description has already been given of the isolation huts which were built in 1937, and of their positions in relation to the main flock (Johnston and Wilson, 1939). The same buildings were still available but required extensive preparation and sterilisation to fit them for our purpose. This was accomplished by cleaning, disinfection and flaming. Certain alterations were made in the buildings to provide each with 4 pens (12 ft. by 14 ft.), storage for a year's food supply, and a system of hinged flaps through which the birds were fed, their eggs collected and any necessary attention given. Through these flaps dead or dying birds were removed with the aid of a sterilised pole and hook.

Great attention to detail was necessary in the flaming of the huts, and the success of the methods we adopted was subsequently proved by the complete absence of coccidia in the fæces of the experimental birds over a period of 10 months.

Floor litter.—Sand derived from a deep sand pit and spread to a depth of 4 to 6 inches was used as litter. Sawdust, which was used in the previous experiment (Johnston and Wilson, 1937, 1939), was considered impracticable since it needed frequent replacement, a fact which increased the possibility of introducing infection.

A preliminary trial with sand as litter had shown that it would disintegrate the fæces and keep the pens moderately dry and comfortable even when not replaced for several months, but there was another equally important consideration. Previous experiments had proved that birds kept inside and run on litter such as sawdust, which must be replaced very frequently, do not build up a heavy infection of either coccidiosis or worms. They also appear to have a lower mortality from fowl paralysis than those kept under the less hygienic conditions which prevail when birds are allowed outside.

This appeared to be the most obvious reason for the comparatively low incidence of the disease in both isolated and non-isolated groups of the previous experiment, which was our first attempt at rearing poultry on a large scale indoors. The coccidial infection accidentally introduced on that occasion was so light that its detection was possible only by taking several samples of fæces at frequent intervals. In the present experiment we hoped that any infection which might be introduced would have an opportunity of developing to such an extent that we should be left in no doubt about its presence.

Stock.—Breeding stocks were carefully selected and mated before the start of the experiment. It was decided to hatch each isolated group from a different breeding pen, in the expectation that this might assist in the interpretation of results. Thus, from the flock of White Leghorns at our disposal two widely different groups were chosen. For the first ("healthy") group, birds were selected from a flock which had suffered very few losses from fowl paralysis; only birds which appeared to be very healthy were selected for breeding. The second ("unhealthy") group was selected from two breeding stocks, isolated and non-isolated, in both of which the incidence of the disease had been fairly high. In this group the selected birds either showed some symptom which was associated with the disease or were closely related to birds of the same age which had died from this cause.

Both sets of parents were subsequently examined *post mortem* for evidence of fowl paralysis. The "healthy" group was killed off immediately after sufficient eggs had been laid. Seven out of 40 hens showed the presence of a small fibroma in the dorsal ligament of the oviduct, but there was no other microscopic evidence of disease. Unfortunately, because so many birds were killed off together, a procedure necessitated by our desire to avoid setting any eggs derived from obviously affected parents, it was not possible to examine these birds histologically.

The "unhealthy" group, on the other hand, were not killed off immediately but were used subsequently as contact birds for the non-isolated controls. Contact birds that died were examined histologically. Of a total of 20 birds examined in this way, none failed to show gross or microscopic evidence of lymphomatosis.

Several precautions were taken to avoid introducing infection to the houses on the surface of eggs. First, only eggs which were completely free from fæces

and stains of blood were retained; second, no eggs which were less than five days old were taken to the isolated unit for incubation; and, third, an attempt was made to disinfect the outside of the eggs by dipping them first in weak tincture of iodine and an hour or so later in a 2 per cent. solution of Dettol. A preliminary experiment showed that no difference could be determined in the hatchability of eggs which had been immersed for a few seconds in 2 per cent. Dettol, hot strong washing soda, alcohol, or weak tincture of iodine. In no case was the disinfecting fluid washed off. The use of 1 : 1000 acriflavine for the same purpose appeared to reduce the hatchability.

The eggs were disinfected outside the isolation quarters and afterwards transferred to the isolation premises and placed in new incubators by an attendant who wore sterile rubber gloves. It should be noted that in the previous experiment chicks were taken into the isolation units at day-old. In the present investigation, when the chicks hatched out, one-third of their number from each isolation unit was removed to the non-isolated control house at the main plant, while the remaining two-thirds were placed under hovers in the isolation pens. Isolated progeny of the "healthy" stock were designated "J," and their non-isolated controls "JC," while the isolated and non-isolated progeny of the diseased birds were afterwards known as "M" and "MC" respectively. The lay-out of the experiment is summarised in Fig. 1.

FIG. 1

Schematic design of experiment to show disposition of isolated and un-isolated experimental chicks derived from "healthy" and "unhealthy" stock.

	Isolation Houses		Control (Non-Isolated) House	
	J	M	JC : MC	
	Group J ("Healthy")	Group M ("Unhealthy")	Group JC ("Healthy")	+ Group MC ("Unhealthy")
Eggs set	508	647	... 0	0
Day-old chicks—				
Hatched	228	149	... 0	0
Transferred		49	———	49
during experiment	76	———	76 +	
Remaining for experiment	152	100	... 125	
Infected adults added	0	0	... 19	

"Healthy" eggs and chicks were derived from selected stock with a few previous losses from fowl paralysis.

"Unhealthy" eggs and chicks were derived from stock selected because of high previous incidence of fowl paralysis.

Food.—While the eggs were incubating, foodstuffs estimated to last one year were delivered to both isolation houses and to the control house. The precautions against introducing fowl paralysis in the food were very thorough. In laboratory studies of coccidiosis sterilisation of the foodstuffs is usually considered essential. In the previous experiment foods of unknown history had been mixed in the store of a commercial firm and delivered each month in new hessian bags, but on an open lorry. It was impracticable to sterilise such a large quantity

of food after delivery. For this experiment we designed our diet with the following points in view: (1) the foods chosen should be subjected to a high temperature during manufacture; (2) the foods should be of such a nature that they would be unlikely to have become contaminated with fowl paralysis; (3) every precaution should be taken to prevent contamination in transit between the manufacturers' premises and the isolation huts; (4) the diet should consist of as few foods as possible; and (5) the diet should promote normal growth and development of birds kept inside. In this connection it is worthy of note that Wilcke *et al.* (1933) have stated that any diet not producing satisfactory growth or sustaining the life of growing birds excited an inhibitory effect upon the development of fowl paralysis. Details of our diet used are shown in table I.

TABLE I.

Standard diet designed to avoid introducing infection.

Time	Foodstuff	Parts
For first 14 weeks ...	Maize meal	65
	Dried yeast	18
	Dried skim milk	12
	Salt	0.5
	Ground limestone	2.0
	Cod liver oil	2.5
	Manganous sulphate	0.0132
	Ferric oxide	0.0625
After 14 weeks ...	Manganese was omitted from the diet.	
After 20 weeks ...	Ferric oxide was omitted from the diet. Ground limestone was increased to 4 parts for the pullets but not for the cockerels.	
After 32 weeks ...	Flaked maize was increased from 65 to 75 parts.	

Grit was available throughout in the sand used for litter.

Special precautions were taken to prevent contamination of the foodstuffs and their containers, both in transit and in store.

General management and routine.—In the previous attempt at isolation each unit had been operated by a special attendant whose duties entailed entering the isolation quarters two or three times a day, and who was obliged to change shoes and superficial clothing on each occasion. In this experiment we operated the units ourselves and limited our entry into the buildings to occasions of absolute necessity—three or four times a week except during the incubation period when twice-daily visits were necessary in order to turn the eggs, and during the time the chicks were under hovers when daily visits were made. As additional precautions we changed all clothing and footwear twice in two separate compartments before entering the houses, and wore rubber gloves and caps to avoid any risk of contamination. The houses were kept locked, thus debarring access to the interior of all persons other than ourselves. Three weeks from the time the chicks were hatched, bi-weekly fæces examinations for coccidia were carried out on mixed samples taken at random from the three houses in the experi-

ment. Absence of coccidia was regarded as evidence that our isolation procedures were still unbroken.

All birds which died or had to be destroyed from any of the three houses were thoroughly examined *post mortem*, and, as a routine, portions of the following organs or parts were transferred to 5 per cent. formol for subsequent histological examinations: liver; heart; kidney; spleen; lung; ovary or testicle; proventriculus; shafts of both femurs; both sciatic nerves; both brachial plexuses; both vagi; brain; and three sections of spinal cord (cervical, thoracic, and lumbar); and any neoplastic tissue. In many cases the thyroid and adrenal glands were also preserved. Portions of these tissues were subsequently dehydrated with dioxane and embedded in paraffin. Sections were cut and stained with hæmatoxylin and eosin. In every instance at least three sections from varying levels of tissue or even separate blocks were examined for the presence of lymphocytic infiltrations or other pathological evidence.

In every liver examined, aggregations of lymphoid cells were noted—a finding in agreement with almost all workers in this subject. Unless these aggregations were of sufficient magnitude to suggest definite evidence of a pathological condition, they were classified as negative. The classification of these lymphoid deposits presented some difficulty, since the diagnosis of a pathological condition on degree or size alone must of necessity be entirely arbitrary. A positive diagnosis was not given if there was any room for doubt, or unless further evidence was forthcoming from examination of some other organ or tissue. Further, in accordance with the observations of Palmer and Biely (1934), confirmatory evidence was sought before small lymphoid deposits in the dorsal root ganglia of a brachial plexus were classified as positive.

Microscopical examination of the brain was later discontinued, because it was frequently observed that if the brain was affected the lesions were distinctly focal and extended over a few serial sections here and there.

Results

From the earliest date coccidia were recovered from the samples of fæces taken from the non-isolated (control) house, where one-third of the chicks originally derived from each isolation hut were running together. (See Fig. 1.) Aided by the unhygienic conditions, the infection reached a remarkably high level and accounted for a number of deaths early in the experiment. Later, helminth eggs were also found in abundance in almost every sample of fæces from this house. During the whole period of eleven months, no coccidia or helminth eggs were observed in any samples of fæces taken from the two isolation houses until the day before the termination of the experiment. On that occasion a light infection of coccidia was found to be present in isolation house J. During the latter part of the experimental period the chitinous carcases of forage acari were observed in the fæces of the control (non-isolated) house, but never in the samples taken from the isolation houses.

The absence of parasites in the fæcal samples from the isolation houses and their presence in those from the control house would suggest that two different groups had apparently been maintained in complete isolation for a period of at least ten months.

Mortality.—For convenience this is considered in three phases: (1) in the egg; (2) from day-old to 8 weeks, when artificial heat is no longer required; and (3) after 8 weeks. It is well known that mortality during the first two periods may be affected not only by the condition of the parent stock, but also by the operation of the incubation and rearing equipment. The mortality is shown in table II.

TABLE II.

Mortality (*deaths from all causes*)

	GROUPS*			
	"Healthy"		"Unhealthy"	
	J	JC	M	MC
No. of eggs set	508	—	647	—
Fertile eggs	436	—	492	...
Mortality during hatching (per cent.)	47.7	—	69.7	—
No. of chicks at day-old	152	76	100	49
Mortality day-old to 8 weeks (per cent.) ...	4.0	15.7	13.0	36.7
No. of birds surviving at 8 weeks	146	64	87	31
Mortality: 8 weeks to 11 months (per cent.) ...	28.1	40.7	17.3	38.7

* "Healthy" = parent stock selected because of low incidence of fowl paralysis
"Unhealthy" = parent stock selected because of high incidence of fowl paralysis
J and M = isolated
JC and MC = non-isolated

It will be observed that hatchability of the eggs set was very poor in both units but particularly so in the unhealthy stock group (M). This was not surprising since some of the eggs in each case had been held for 28 days and the freshest had been laid for five days before being placed in the incubator because of a fall in production during the collecting period. Eggs over 18 days old did not hatch well.

It was intended to have at least 150 birds in each isolation unit (J and M) and in the non-isolated control house (JC and MC together). This figure was reached satisfactorily in house J; but in house M, because of difficulties beyond our control, the number of chicks fell far short of requirements and was further heavily depleted during the rearing period. At 8 weeks this group was little more than half the size we had hoped for.

It will be observed that the eggs from the "unhealthy" hens had a lower hatchability, and the chicks which hatched (M and MC) were of lower vitality than those derived from the "healthy" stock (J and JC). It is not possible to say whether this result was due to the influence of the parent stocks or to use of separate incubators. After hatching, an ideal comparison was provided in the control house where JC and MC birds, after being marked for identification, were run together. The mortality in the "unhealthy" (MC) group was more than twice that in the "healthy" (JC) group. During the subsequent period, which is the critical phase in a study of fowl paralysis, the mortality was practically the same in each of the control groups.

In the isolated units rearing mortality was in each case about one-third that

of the controls; but from 8 weeks to the end of the experiment mortality was considerably higher in the isolated "healthy" group (J) than in the isolated "unhealthy" (M).

Post-mortem Diagnosis

The incidence of lymphomatosis (fowl paralysis) and its relation to mortality is given in detail in Table III.

TABLE III.

Mortality from lymphomatosis (fowl paralysis), leukæmia, and other causes.

	No. of day-old chicks at start of experiment.	No. dead at 3 weeks.	No. dying from 3-8 weeks.		No. dying from 8 wks.-11 mths.			Total mortality from day-old - 11 months.			Total mortality (%) from fowl paralysis from 3 wks.-11 mths.
			Fowl paralysis.	Other causes.	Fowl paralysis.	Leukæmia.	Other causes.	Fowl paralysis.	Leukæmia.	Other causes.	
Isolation, healthy (J)	152	6	0	0	33	5	3	33	5	9	22.6
Isolation, unhealthy (M) ...	100	12	0	1	1	1	13	1	1	25	1.1
Non-isolated, healthy (JC) ...	76	3	5	4	22	1	3	27	1	10	37.0
Non-isolated, unhealthy (MC)	49	8	1	9	7	0	5	8	0	22	19.5

The chief interest in this table is the comparative incidence of lymphomatosis in the two isolation houses. In house J ("healthy" group) the incidence was high (22.6 per cent.), whereas in house M ("unhealthy" group) the incidence was almost insignificant (1.1 per cent.).

Lymphomatosis was first diagnosed in the non-isolated control house among the "healthy" (JC) birds, as a clinical case in a pullet 44 days old. Thereafter eight birds of this group, including five clinical cases, and three in the "unhealthy" group (MC), including two clinical cases, showed evidence of lymphomatosis before the first case appeared in isolation in house J at the end of 98 days.

An analysis of the post-mortem findings is given in Table IV. In most instances several pathological conditions were found in a single individual and such findings have been included in two or more groups. This method of analysis conforms to that used in the previous experiments of Johnston and Wilson (1937, 1939) and enables a comparison to be made.

The most striking point in the evidence in Table IV is the high incidence of leucotic conditions—up to 26 per cent.—among the "healthy" birds in isolation house J, compared with only 2.3 per cent. in the "unhealthy" birds from isolation house M. These differences are still more striking if the incidence of leucotic conditions is based on total mortality after the first three weeks: 93 per cent. of the deaths in house J and 12.5 per cent. of those in house M were attributable to leucotic infection. Comparison of the two non-isolated control groups again reveals a much higher incidence of leucosis in the "healthy" JC group: almost double that for the "unhealthy" MC birds. When based on total mortality after the age of three weeks the leucotic incidence is 80 per cent. for JC as against 36 per cent. for MC.

TABLE IV.

Analysis of post-mortem findings.

	Isolated healthy birds (J)	Isolated unhealthy birds (M)	Non-isolated healthy birds (JC)	Non-isolated unhealthy birds (MC)
3 weeks to 11 months.				
Total No. of birds at 3 weeks	146	88	73	41
Injury and accident ...	3 (2.1%)	3 (3.4%)	2 (2.7%)	2 (5.0%)
Peritonitis, prolapse, etc.	1 (0.7%)	0	2 (2.7%)	1 (2.4%)
Leucosis (Macroscopic including leukæmia, fowl paralysis and tumours)	26 (17.9%)	1 (1.1%)	17 (23.3%)	5 (12.2%)
Leucosis (Microscopic)	38 (26.0%)	2 (2.3%)	28 (38.3%)	8 (19.5%)
Rupture of tendons ...	9 (6.2%)	8 (9.1%)	2 (2.7%)	0
Impaction of digestive tract	0	2 (2.3%)	7 (9.6%)	6 (14.6%)
Atrophy and degeneration of organs ...	0	1 (1.1%)	2 (2.7%)	0
Nephritis	1 (0.7%)	0	0	2 (5.0%)
Coccidiosis	0	0	0	4 (9.8%)
Other causes	3 (2.1%)	0	2 (2.7%)	2 (5.0%)
8 weeks to 11 months.				
Total No. of birds at 8 weeks	146	87	64	31
Injury and accident ...	3 (2.1%)	3 (3.4%)	2 (3.1%)	2 (6.5%)
Peritonitis and prolapse	1 (0.7%)	0	1 (1.6%)	1 (3.2%)
Leucosis (Macroscopic including leukæmia, fowl paralysis and tumours)	26 (17.9%)	1 (1.2%)	13 (20.3%)	4 (12.8%)
Leucosis (Microscopic)	38 (26.0%)	2 (2.3%)	23 (36.0%)	7 (22.5%)
Ruptured tendons ...	9 (6.2%)	8 (9.2%)	2 (3.1%)	0
Impaction of digestive tract	0	1 (1.2%)	3 (4.7%)	0
Atrophy and degeneration of organs ...	0	1 (1.2%)	2 (3.1%)	0
Nephritis	1 (0.7%)	0	0	2 (6.5%)
Coccidiosis	0	0	0	1 (3.2%)
Other causes	3 (2.1%)	0	2 (3.1%)	2 (6.5%)

The earliest case of paralysis was diagnosed clinically 44 days from the time of hatching. No typical cases of clinical paralysis were found among the "unhealthy" birds in isolation house M, though both here and in the other houses several pale or decolourised eyes were observed.

Table IV includes a new category, "Rupture of tendons," not previously observed by Johnston and Wilson.[1] This condition, whose cause is unknown, will be reported separately in a later contribution (Harriss, 1947).

Both cases diagnosed as leucosis in the "unhealthy" birds in isolation house M are open to discussion and the findings in these birds are therefore given in detail.

Case 1. *No. A191.*—White Leghorn Cockerel. Age 7 months. In poor condition.

History.—Bird has been backward since hatching. Legs have been affected for seven weeks.

Symptoms.—Both legs bent stiffly. Left leg worse than right. Bird walks on point of left hock with toes slightly curled inwards. Right leg has a marked tremor when moved. Iris of right eye is slightly grey round pupil and the pupil itself is distorted.

Post-mortem.—Left Achilles tendon almost ruptured proximal to point of hock. Only a weak shred of tendon remains. Right Achilles tendon is torn apart longitudinally. The cartilaginous articular area in contact with the surface of the trochlea of the femur is marked by a jagged break. This tendon is markedly thickened proximal to the affected area. No inflammatory reaction is present.

Histology.—Slight round-cell infiltration of heart muscle. Both Achilles tendons show changes typical of rupture and sprain.

Case 2. *No. A323.*—White Leghorn Cockerel. Age 9 months. In fair condition.

History.—Found dead.

Post-mortem.—Liver and spleen grossly enlarged and mottled. Kidneys slightly enlarged and lightly mottled. Medullary cavities of long bones greatly reduced in diameter; osseous tissue in hyperplastic. Marrow is pale grey in colour.

Histology.—Liver, spleen and kidney show typical engorgement of capillaries with round cells. Almost complete absence of liver cells. Blood (taken from clot in heart) shows preponderance of immature forms.

During the course of the experiment the bowel contents of a number of fowls which had died or were removed from both isolation houses were examined by Dr. J. Smith, Aberdeen City Hospital, for the presence of *Salmonella* organisms, always with negative results. We therefore found no evidence in support of Emmel's (1937) view that the presence of *Salmonella* infection is an essential part of fowl paralysis.

At the conclusion of the experiment all birds were removed from both isolation houses and transferred to the control house after it had been thoroughly cleaned. Within a week after the transfer a high mortality from coccidiosis developed in the birds which had formerly been in isolation. Cockerels in particular appeared highly susceptible and succumbed rapidly. It had been decided to dispose of all cockerels from isolation house J for reasons of economy, but their sale could

not be completed before four cockerels had died after showing evidence of acute coccidiosis. Nine pullets from this house died within six weeks from the same cause.

It was hoped that the remnants of isolation house M birds might provide a useful stock for further experiments, but for reasons connected with the outbreak of war it was not possible to maintain them in isolation. After their transfer to the control house, 21 cockerels—the whole of the surviving males from house M—and five pullets died from coccidiosis.

At the time of the transfer a comparison of the quarters occupied by the birds of houses J and M were made. Both houses were in an extreme condition of filth and the air was so heavy with the fumes of ammonia that the eyes smarted. House J, which had carried the larger number of birds, was in a worse state than house M. It appeared damper throughout and had a heavier content of fæcal material.

Discussion

Our isolation technique was extremely strict because previous experience had convinced us that the utmost precautions were necessary for successful isolation of a large number of birds over a long period of time. The breakdown in isolation shown by the appearance of coccidiosis after 11 months is further evidence that our attention to detail was not over-emphasised. Our success in maintaining the stock of birds for 11 months under conditions of practical isolation proved adequate for our purpose, since it was primarily intended to study the effect of isolation on the incidence of lymphomatosis. The presence of oocysts, helminth eggs and the carcases of forage acari in the fæces of the birds in the non-isolated control house was in marked contrast to the negative findings in the fæces of the isolated birds. It is evident also that lymphomatosis may occur in the total absence of intestinal parasites. With the absence of coccidia as our criterion for successful isolation, the appearance of lymphomatosis in the isolated stock some eight months before the breakdown of isolation suggests that the infective agent of lymphomatosis need not depend on external influences for its transmission—a further substantial argument, though not absolute proof, in favour of the theory of transmission of the virus through the egg. The much earlier appearance of clinical symptoms of paralysis and its much higher incidence in non-isolated birds might be attributed to intestinal parasitism or to the presence in the non-isolated house of 19 infected adults. Eight clinical cases of paralysis appeared and four others were demonstrated histologically among the non-isolated birds before the first case, a clinical one, appeared among the isolated birds.

To explain the high incidence of lymphomatosis among the progeny of the "healthy" parents, and the comparatively low incidence in the offspring of the "unhealthy" birds, it must be remembered that the parents of the birds in groups J and JC, though clinically free from the disease when selected, were yet derived from a stock in which lymphomatosis had been present although its incidence had been low. It is possible that some or all of the parent birds had become infected as chickens but had never shown clinical evidence of the disease, and it may be that low incidence in the flock was associated with and perhaps the cause of low resistance in the progeny from a low degree of inherited immunity. This immunity

may have been sufficient to prevent the appearance of disease symptoms in the adult birds but insufficient to exclude the presence of carriers.

The question of the carrier bird is one that has not yet received sufficient consideration in lymphomatosis research. Transmission *via* the egg, though not definitely proved, has for long been accepted as a common means of spreading the disease. Gibbs (1936) has expressed the view that neuro-lymphomatosis is usually not transmitted through the egg unless the ovary of the hen or the testis of the cock is infiltrated, but if the virus is present in the blood stream, infection of the ovary and consequently the egg would be the expected sequel. Virus has not yet been demonstrated in the blood stream of apparently healthy birds, but it has been found in the blood of clinical cases by Jungherr (1937), Blakemore (1939), Furth (1935) and others, though Olson (1936-37) was unable to substantiate these claims.

Blakemore (1939) has shown that by breeding from infected birds for several generations, and by maintaining the offspring in practical isolation, he was able to produce a stock which he considered free from lymphomatosis although still highly susceptible.

Such a process may explain the phenomena encountered among the "unhealthy" (M) birds and their non-isolated controls (MC). The two positive cases of leucosis in these birds, of which the *post-mortem* findings have already been recorded in this paper, were at the best only slender evidence of fowl paralysis in this group. One of the cases (A323) was a typical case of leukæmia, and the second (A191) showed only slight infiltration of the heart muscle and a typical lymphomatosis pupil. It is possible that one or other of the parent birds of house M, acting as a carrier, transmitted the virus *via* the egg, and this would account for the lesions in A191, but it is evident that some influence was at work to prevent the spread of the virus among the remainer of the birds in that house. It should be noted that the classification we have adopted in grouping the leucotic diseases in Table IV is in conformity with the previous experiments of this series (Johnston and Wilson, 1937, 1939). From the work of Engelbreth-Holm (1932), Furth (1931, 1933, 1934, 1935, 1937), Gibbs (1933, 1934, 1936), Jarmai (1934), Jungherr (1937), Schaaf (1936), and Stubbs (1931), there is sufficient evidence to show that the leukæmias of fowls and lymphomatosis are separate disease entities. If this is accepted, only one case of lymphomatosis was diagnosed in house M. This freedom among the progeny of infected hens (group M), though not absolute, was none the less remarkable, and persisted throughout the period from 8 weeks to 11 months, which covers the highest age-incidence of the natural disease. Most writers are agreed that eggs from an infected flock should not be used for breeding purposes. For example, Beaudette and Black (1934) reported a higher incidence of fowl paralysis in the offspring of paralysed birds than in those of apparently free birds. But they made no attempt to rear the chicks away from infected premises. On the other hand, Blakemore (1939) has shown that the rearing of chicks hatched from an infected flock resulted in the disappearance of the disease in three generations if the chicks were reared in isolation under conditions which offered no chance of re-infection, and he actually adopted this procedure to provide a source of fowl paralysis-free birds for experimental purposes. It is significant that the resulting stock was highly susceptible to fowl

paralysis. The evidence from group M in our present experiment appears to support this method of controlling the disease. It seems reasonable to suggest, therefore, that if hatching-eggs from a fowl-paralysis-free stock are difficult or impossible to obtain, healthy birds may yet be reared from eggs laid by an infected flock, provided the chicks are removed to clean ground or premises and maintained there with efficient precautions to prevent re-infection.

Summary and Conclusions

1. The technique of maintaining successfully a large number of birds under conditions of isolation is described. Two hundred and fifty-two birds were put under isolation which was maintained for a period of 11 months, the absence of coccidial oocysts from the fæces being used as the criterion for successful isolation.

2. A high incidence of leucosis (26 per cent.) was found in isolated birds hatched from apparently healthy parents. A very low incidence (2.3 per cent.) was recorded among the progeny of already infected parents. Correspondingly higher but comparable results were obtained among full brothers and sisters of these birds kept in non-isolated circumstances for control purposes (38.3 per cent. and 19.5 per cent., respectively).

3. The appearance of fowl paralysis (lymphomatosis) in spite of complete isolation is strong evidence in favour of egg transmission.

4. A comparatively high incidence of rupture or "sprain" of the tendo Achilles was observed in all groups. It did not appear that this condition bore any relationship to fowl paralysis.

5. A vitiated atmosphere and unhygienic conditions may be contributory causes but are not the primary factor in the production of leucosis.

6. No age immunity to coccidiosis develops in the absence of the infective agent. Fowls over 11 months old succumbed rapidly to coccidiosis when removed from isolation. Cockerels appeared more susceptible than pullets.

7. No evidence was obtained which was inconsistent with the theory of a virus infection in lymphomatosis.

8. There is strong evidence that the progeny of infected parents are resistant.

We wish to express our indebtedness to Professor T. Dalling and Professor D. M. S. Watson, of the Agricultural Research Council, for helpful advice and criticism, to Dr. J. Smith, of the City Hospital, Aberdeen, for assistance in attempting to isolate various organisms, and to Mr. J. E. Wilson, of the Poultry Laboratory, Ministry of Agriculture and Fisheries, Lasswade, for valuable assistance from time to time.

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A MODIFIED BIOLOGICAL METHOD FOR ESTIMATING THE ACTIVE PRINCIPLES OF MEDICINAL AND POISONOUS PLANTS AND PREPARATIONS MADE FROM THEM

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Introduction

THE usual chemical and gravimetric methods of assay employed for the separation, purification and estimation of the active principles of crude drugs are sometimes tedious and expensive. The present writer in the course of his investigations into the Egyptian plant, *Euphorbia peplus,* was led to develop a modified biologic method for the quantitative estimation of these active principles, which cannot now be satisfactorily estimated by the older methods.

The determination of the active and toxic principles of the medicinal and of the poisonous plants should be, as far as possible, thorough and complete. The present writer, therefore, intends to employ the biologic method now to be described, besides the usual gravimetric method, to estimate accurately the active and toxic principles of as many as possible of the plant materials in Egypt, known or suspected to have a medicinal or toxic action upon animals. He hopes then to find out to what extent these two methods of assay (the chemical and the biological) differ from each other.

The biological methods commonly employed, whether for comparison of

activity or for standardisation, differ largely in so far as they have been carried out on different species of animals. Different individual animals of a given species have again been employed in each estimation in these different methods. These variations in method entail discordance in the results obtained, arising through variability in response as among the several species and again among the different individuals of a given species. In the modified method devised by the writer, the separate pharmacological or toxicological effects of the several active principles extracted from a given plant are determined upon one animal only. This avoids the difficulty arising from variability among the animals, when a different animal or group of animals, is employed to determine the effect of each separate principle.

A Brief Description of the Method

The method consists in comparing biologically the effect, say on the blood pressure, of a known weight, say 0.5 g., of the extract of a given plant or plant preparation, with that of the active constituent or of the several separate active constituents isolated from this same weight of that original extract. Dilutions of purified samples in solution, each sample corresponding with the active principles isolated from the extract, are then injected in gradually increasing doses until the same effect is produced on the blood pressure as was produced by the amount of active principles as isolated from the above quantity of crude extract.

Dogs were chosen for the experiments. The dog used in an experiment was first anæsthetised by ether inhalation. The anæsthesia was then maintained by injecting warm chloralose solution intravenously into the femoral vein, in doses of 0.1 g. per kg. live body weight. The blood pressure was recorded from the carotid artery, through a cannula containing a half-saturated solution of sodium sulphate, by means of a lever carrying a point writing on a kymograph drum paper. The drug solutions were injected intravenously into the femoral vein. The injections were always followed by 2 c.c. of saline solution to wash the whole of the drug out of the cannula into the vein.

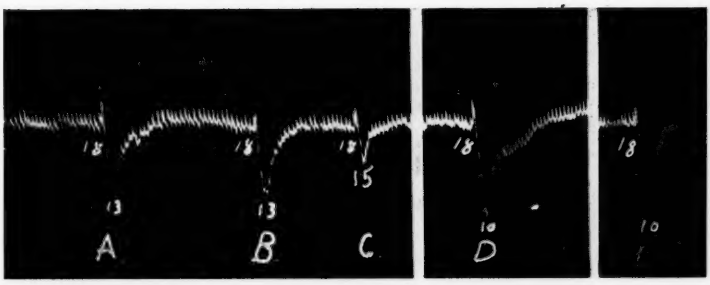
Application of the Method

The method was satisfactorily applied in estimating the active constituents of the Egyptian plant, *Euphorbia peplus,* and in comparing these estimated amounts with those of these constituents estimated gravimetrically.

1. *Preparation of an alcoholic extract of* Euphorbia peplus *and isolation of the active principles in this extract by gravimetric methods, for comparison with the estimations of these active principles by the modified biological method.*

(a) The dried finely powdered plant was packed in a continuous extraction apparatus after moistening with 10 per cent. saturated ammonia solution dissolved in 95 per cent. alcohol. It was then extracted with alcohol until completely exhausted. The liquid was taken and the alcohol evaporated away from it leaving a dry residue weighing 22.5-25 per cent. of the original dried plant powder.

(b) A resin, an alkaloid and a glucoside were detected in this dried alcoholic extract. Each was then separated. The resin was found to amount to about 31 per cent. by weight of the extract, or 7.5 per cent. of the original plant powder. The alkaloid was found to amount to about 0.5 per cent. of the dried alcoholic



Kymograph Tracing showing the effects of the Alkaloid and Glucoside isolated from Euphorbia peplus.

(a) & (b) Showing the fall in arterial blood pressure in a dog injected into the femoral vein with the glucoside in 0.5 g. of the alcoholic extract (= 25 per cent. of the whole dried plant powder).
(c) Showing fall in blood pressure produced in the same dog by the alkaloid in the same quantity of the alcoholic extract.
(d) Showing the effect on the same dog of the above quantity, i.e., 0.5 g., of alcoholic extract, after removal of the resin, i.e., containing its alkaloid and glucoside.
(e) Showing the effect on the same dog of the combined purified glucoside and alkaloid in amounts corresponding with those present in the above quantity of extract.

extract, or 0.13 per cent. of the original powdered plant. The glucoside was found to amount to about 11.8 per cent. of the dried alcoholic extract, or 2.9-3 per cent. of the powdered plant.

2. *Solutions were prepared and injected as follows*:

Solution No. 1.—Dried alcoholic extract, 0.5 g., after removal of its resin, was injected to find out the effect of the alkaloid and glucoside in combination in this quantity of extract. The resin was removed as it would otherwise vitiate the experiment, because of its insolubility in a watery medium and hence its liability to cause arterial thrombosis.

Solution No. 2.—Dried alcoholic extract, 0.5 g., after removal of its resin and its alkaloid, was injected to find out the effect of the glucoside only in this quantity of extract.

Solution No. 3.—Dried alcoholic extract, 0.5 g., was subjected to alkaloid extraction, and the slightly acidic solution of the separated alkaloid was injected to find out the effect of the alkaloid only present in this quantity of extract.

Solution No. 4.—A 1 : 80 dilution of the separated purified glucoside was injected in gradually increasing doses until an effect was produced on the blood pressure nearly similar to that of solution No. 2.

Solution No. 5.—A 1 : 200 dilution of the separated purified alkaloid was injected in gradually increasing doses until an effect was produced on the blood pressure nearly similar to that produced by solution No. 3.

3. *Results.*

The above solutions were injected with the following results:

Solution No. 1 produced a fall in blood pressure of about 80 mm. of mercury.

Solution No. 2 produced a fall in blood pressure of about 50 mm. of mercury.

Solution No. 3 produced a fall in blood pressure of about 30 mm. of mercury.

Solution No. 4. This 1 : 80 glucosidal solution was injected in small, gradually increasing doses, and when the amount injected had reached 5 c.c., nearly the same effect was produced on the blood pressure as with solution No. 2. Therefore, the quantity of glucoside present in 0.5 g. alcoholic extract is equivalent to that present in 5 c.c. of a 1 : 80 solution of the known glucosidal solution. Hence, 5 c.c. of a 1 : 80 solution, or 0.0625 g., of the known glucoside corresponds with the glucoside present in 0.5 g. of the alcoholic extract of the powdered plant. That is, the powdered plant contains about $\frac{1}{4} \times 2 \times 0.625 \times 100 = 3.125$ per cent. of glucoside.

Solution No. 5. This 1 : 200 alkaloidal solution was also injected in small, gradually increasing doses until it was found that nearly the same effect was produced on the blood pressure when 0.5 c.c. had been injected as was produced by solution No. 3. Hence, 0.5 c.c. of a 1 : 200 solution, or 0.0025 g., of the known alkaloid corresponds with the alkaloid present in 0.5 g. of the alcoholic extract of the powdered plant. That is, the powdered plant contains about $\frac{1}{4} \times 2 \times 0.0025 \times 100 = 0.125$ per cent. of alkaloid.

4. *Conclusion.*

(a) The alkaloid and glucoside isolated from the Egyptian plant, ***Euphorbia peplus,*** have a similar effect on the blood pressure, as determined by the method

recorded in this paper, to corresponding doses of the crude alcoholic extract (after resin removal), indicating that the active principles are entirely the alkaloid and the glucoside.

(b) As estimated by this method, the glucoside amounted to 3.125 per cent. and the alkaloid to 0.125 per cent. of the dried powdered plant. These figures correspond closely with those obtained by gravimetric methods.

(c) This method is suggested for application by the pharmacologist:

(1) For detecting the presence of the active principles in a given extract;

(2) For determining the relative toxicity of the several active principles isolated from a poisonous plant, so as to identify the lethal principle;

(3) For estimating the activity of pharmaceutical preparations of unknown strength;

(4) For the examination of old pharmaceutical preparations to ascertain to what extent they have retained their efficacy; for detecting the purity of fresh pharmaceutical preparations, etc.

Acknowledgment

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OBSERVATIONS ON THE USE OF "INTRAVAL SODIUM"

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THE product "Intraval Sodium" is the trade mark of soluble Thiopentone B.P. produced by Messrs. May & Baker, Ltd. It is chemically the same as "Pentothal Sodium" produced by Abbott Laboratories, Ltd., viz., sodium ethyl (1-methyl butyl) thiobarbiturate. The drug is supplied as hygroscopic crystals in glass phials, together with enough sterile water to make a 5 per cent. solution. It is freely soluble at ordinary temperatures. Two packs are at present available, a 0.25 gramme (3.75 grs.) suitable for inducing anæsthesia in cats and a 0.5 gramme (7.5 grs.) size suitable for use in the dog.

Observations have been made on a limited number of subjects only, where "Intraval Sodium" has been employed as the anæsthetic agent in the dog, cat and horse.

In the small animal.—The drug has been used quite extensively in both the dog and cat for operations of short duration, and in a small number of cases data relating to its use has been collected. The drug has proved to be a safe,

short-acting anæsthetic, having been used in both the very young and old subject without mortality accompanying its use. Even when administration is repeated the drug is well tolerated.

Administration.—The anæsthetic was administered in 5 per cent. solution by slow intravenous injection. In the majority of cases the anæsthetic dose was given over a period of 3½ to 4½ minutes. Where an assistant was available, however, it has been given over a longer period, throughout the period of operation very satisfactorily.

Generally, the more slowly the drug is administered the longer the period of anæsthesia and less danger of respiratory failure. On an average the period of 4 minutes proved to be the most satisfactory. It was found that rapid injection of the solution resulted in a very short period of anæsthesia, with a tendency to respiratory failure with comparatively small doses.

Dosage.—The dosage required varies quite considerably, and is largely dependent on the rate of administration. Comparatively large doses are tolerated if the period of administration is sufficiently long. Deep anæsthesia can be produced by surprisingly small doses if administration is fairly rapid. Where the period of administration was about 4 minutes an average dosage of 1/7 to 1/5 gr. per lb. body weight was necessary.

Anæsthetic action. — The narcotic action of "Intraval Sodium" is very marked, a small percentage of anæsthetic dose is sufficient to cause muscle relaxation and the animal becomes unable to stand at an early stage. The state of narcotic excitement during administration of intravenous anæsthetics, which is very easily induced with other barbiturates, is conspicuously absent when this drug is used. One has been unable to produce narcotic excitement with "Intraval Sodium" in the dog and cat. The respirations are markedly depressed and if administration is at all sudden, especially when the subject is in a state of deep narcosis, respirations cease. The effect is, however, transient and artificial respiration has on all occasions been sufficient to cause spontaneous breathing to begin.

On the few subjects where it has been observed, the pulse rate increases up to twice normal during induction and during the recovery period, but during the state of surgical anæsthesia it is only slightly above normal rate.

The period of surgical anæsthesia was regularly 10 minutes, if the anæsthetic dose was all given over a period of 4 minutes. The duration of anæsthesia varies with the rate of administration. The state of the animal during anæsthesia is one of complete muscular relaxation, with depressed and abdominal respirations. As the drug is eliminated there is a state of deep narcosis and the reflexes begin to reappear; this lasts about 10 minutes. The animal then begins to move, and may show something approaching narcotic excitement as recovery proceeds; it is a period of about 30 to 40 minutes, commencing with shivering, galloping movements of the limbs, lifting head, sitting up, and terminating with the animal standing, usually with the four legs apart. The subject is usually standing thus within an hour of administration.

Indications.—"Intraval Sodium" has proved most satisfactory for operations of short duration on the dog and cat with no death attributable to its use. In

particular, dental operations, removal of foreign bodies from pharynx, examination of mouth, hæmatoma of ear flap, palpation of abdomen and limbs, reduction of dislocations, radiography, opening of an abscess, can be performed using this anæsthetic. Very adequate anæsthesia can be maintained for operations of longer duration by successive small doses as anæsthesia lightens.

Comparison with other barbiturates.—In a limited number of cases one has been able to compare the anæsthetic action of "Intraval Sodium" with that of "Pentothal Sodium" and "Nembutal" in the same subject.

In the subjects Case No. 7 and No. 10 the dosage of "Pentothal" was very slightly smaller, the period of anæsthesia 2 to 4 minutes longer and recovery period slightly more prolonged.

In Case No. 8 and No. 6 opportunities arose to use "Nembutal." In Case No. 8 the state of anæsthesia persisted for 40 minutes, as compared with 8 minutes with "Intraval Sodium." The dosage of "Nembutal" was 1/5 gr. per lb. B.W. and that of "Intraval Sodium" $\frac{1}{8}$ gr. per lb. B.W.

In Case No. 6 "Nembutal" produced anæsthesia for 5 hours—with a dose of 1/5 gr. per lb. B.W. A dose of 1/7 gr. per lb. B.W. of "Intraval Sodium" was used, producing anæsthesia of 10 minutes' duration.

Case Records

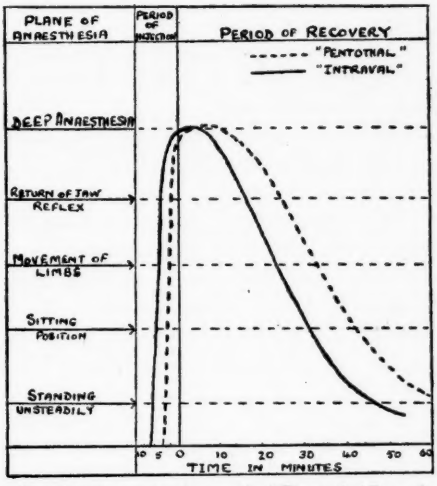
In the Dog:

Case No. 3: Lakeland Terrier aged 11 years, weight 30 lb., with hæmatoma of ear flap. $1\frac{1}{2}$ grs. was injected over a period of $\frac{1}{2}$ minute, the animal lost use of legs, and muscles relaxed, all reflexes brisk, tongue curled, and yawning. A further $2\frac{1}{4}$ grs. were given over the next $3\frac{1}{2}$ minutes and a state of deep anæsthesia was produced, with complete muscle relaxation, loss of reflexes, including the pedal reflex. Anæsthesia persisted for 10 minutes. After a further 10 minutes shivering and shaking head. 10 minutes later trying to sit up. 1 hour after administration the dog was standing unsteadily. A total of $3\frac{3}{4}$ grs., i.e., approximately 1/7 gr. per lb. B.W.

Case No. 6: Staffordshire Bull Terrier aged 3 years, weight 28 lb., with simple fracture of left tibia. A total of 4.9 grs. was injected over a period of 3 minutes, producing anæsthesia lasting 10 minutes. Recovery to state of narcotic inco-ordination was reached in 25 minutes. A total of 4.9 grs., i.e., 1/7 gr. per lb. B.W.

Case No. 7: Alsatian dog aged $2\frac{1}{2}$ years, weight 92 lb. History of distemper 6 weeks previously with a resulting circling to the left. Otherwise normal good bodily condition. Both "Pentothal Sodium" and "Intraval Sodium" were used in this subject. "Intraval Sodium" was administered after 12 hours' fasting. 5 grs. were given over a period of 40 seconds, loss of ability to stand, but able to move head. 8 grs. were then given over a period of 5 minutes, resulting in gradual onset of anæsthesia, until the pedal and corneal reflex had gone. There was no state of narcotic excitement. The animal was allowed to lie in lateral recumbency. After 10 minutes there were strong corneal and pedal reflexes present. In 12 minutes could move head. After 20 minutes, whining and able to sit up, with most power in fore-quarters. 25 minutes—slight excitement,

irregular swinging of head and movement of fore-quarters. 30 minutes—restless; not able to stand. 60 minutes—standing unaided. Total dose 13 grs., i.e., 1/7 gr. per lb. B.W. After 48 hours on normal diet, "Pentothal Sodium" was administered under similar conditions; 5 grs. were given within 30 seconds, a further 2.5 grs. in 40 seconds and administration continued until a total of 12 grs. had been administered over a period of 4½ minutes. This produced deep anæsthesia, with loss of corneal and pedal reflexes, pinpoint pupil. Deep anæsthesia persisted for 15 minutes, at the end of which there was a brisk corneal and pedal reflex. In 20 minutes the jaw reflex and palpebral reflexes were returning; pupil normal. 25 minutes—the jaw reflex strong with curling of tongue; voluntary opening of eyes. 30 minutes—not able to lift head; irregular respirations. 32 minutes—mouth, tongue active, licking lips and swallowing. 40 minutes—stretching of limbs; not able to lift head. 55 minutes—able to stand with assistance. 65 minutes—able to walk with a degree of swaying, especially of hind limbs.



Graphical comparison of "Pentothal" and "Intraval Sodium" anæsthesia (Case No. 7).

Case No. 8: Mongrel Spaniel, 2 years old, weight 35 lb., with blocked nasolachrymal ducts. A total of 4½ grs. was given over 4½ minutes, producing state of medium anæsthesia. 5 minutes after end of injection there was return of jaw and pedal reflex. At 8 minutes there was movement of the head. A further ¾ gr. was given and anæsthesia persisted for 10½ minutes. 1 gr. more caused it to last a further 10 minutes. ¾ gr. produced anæsthesia, again lasting 10 minutes. Thus a total of 7 grs. were used to produce anæsthesia persisting for 30 minutes. The initial injection was at the rate of ⅛ gr. per lb. Total of 7 grs., i.e., 1/5 gr. per lb.

Case No. 9: Mongrel Terrier, 18 months old, weight 28 lb. Normal dog. A total of 6 grs. was given over a period of 10 minutes, producing deep anæsthesia, which persisted for 8 minutes, after which the pedal reflex returned. At 10 minutes the jaw reflex returned. 20 minutes—licking lips; shaking head; galloping movements with limbs. The respirations were depressed from 40 per minute before anæsthesia to 18 per minute in deep anæsthesia. The pulse rate before anæsthesia was 85 per minute, rising to 150 per minute during induction, and becoming regular at 90 per minute during deep anæsthesia, rising again to 130 during the period of recovery. A total of 6 grs., i.e., approximately 1/5 gr. per lb. B.W.

Case No. 10: Fox Terrier, aged 3 years, weight 17½ lb. Normal dog. A total of 4½ grs. was given over a period of 4 minutes. Deep anæsthesia lasted for 10 minutes. By 12 minutes the pedal reflex had become brisk, and on

opening the jaws a yawn was produced. After 30 minutes voluntary movement of the head, shivering. At 55 minutes standing unsteadily. Total 4½ grs., i.e., approximately ¼ gr. per lb. B.W.

In the Cat:

Case No. 1: Tabby cat, aged 13 years, weight 11 lb. Normal cat. ¾ gr. caused the cat to assume recumbency; reflexes brisk; respirations slowed. 1½ grs. caused a cessation of respirations and sluggish reflexes. Administration was continued for 4 minutes and ¼ gr. doses were given until a total of 3 grs. had been administered. Respirations were very depressed and although they ceased on occasions, artificial respirations caused them to recommence. A total dose of 3 grs., i.e., ¼ gr. per lb. B.W.

Case No. 2: Black cat, aged 8 years, weight 15 lb. Hæmatoma ear flap. ⅜ gr. was sufficient to cause loss of power in limbs, and cat assumed recumbency. 1 gr. caused a temporary cessation of respirations and the reflexes became sluggish. Small doses were given till a total of 1¾ grs. had been administered over a period of 3½ minutes. There was a return of reflexes in 9 minutes. Recovery was rapid, moving head in 20 minutes, standing in 50 minutes. Total dose 1¾ grs., approximately ⅛ gr. per lb. B.W.

Case No. 4: Tabby male cat, aged 4 years, weight 11 lb. For operation of castration. An initial dose of ¾ gr. caused the animal to drop, it started vomiting movements, but no gastric contents were expelled and the tongue became cyanotic. This phase quickly passed off after an approximate duration of 30 seconds. 1½ grs. caused a cessation of respirations and artificial respiration was necessary. A total of 1¾ grs. were sufficient to produce deep anæsthesia, given over a period of 3 minutes. The period of anæsthesia was 10 minutes. After 20 minutes—shaking head and strong reflexes. In 30 minutes—shivering; stretching; tongue curling; salivation and swallowing. Full recovery within 1 hour. Total dose 1¾ grs., approximately 1/6 gr. per lb. B.W.

Case No. 5: Black male cat, aged 2 years, weight 10 lb. Abscess on R.H. limb. Slow injection over 2 minutes of 1½ grs. caused complete recumbency and temporary cessation of respirations. Within the next minute ¼ gr. was administered, making a total of 1¾ grs. in 3 minutes. Recovery commenced after 12 minutes. Total dose 1¾ grs., i.e., approximately 1/6 gr. per lb. B.W.

In the Horse:

"Intraval Sodium" has been used on two horses which were for destruction, and the case reports illustrate the results obtained. In Case No.1—the results obtained are misleading owing to the fact that administration was not performed sufficiently accurately. In Case No. 2—administration was performed slowly and carefully, in order to produce surgical anæsthesia. A state of narcotic excitement characterised the induction and recovery stage in both cases, and in neither case did the animal assume recumbency quietly as in chloral hydrate narcosis or as with "Intraval Sodium" anæsthesia in the dog. Surgical anæsthesia was produced in Case No. 2 with, approximately, ⅛ gr. per lb. B.W. It was characterised by complete muscular relaxation and painful stimuli did not evoke any response. The respirations, as in the small animals, were depressed, and in deep anæsthesia were often Cheyne-Stokes in nature. It was apparent that once the animal was anæsthetised, that state could be maintained by repeated small injections very

easily. Once the administration had ceased, recovery occurs rapidly, as in the dog. Total period of anæsthesia following a single injection was ten minutes.

Case No. 1: Grey, aged Pony Mare, weight calculated from measurements $\frac{\text{length} \times \text{girth}^2}{300} = 513$ lb. Normal in health. Prior to injection: temperature 100 deg. F., pulse 52/min., resp. 13/min. Anæsthesia: The anæsthetic used was M & B "Intraval Sodium," a solution of 100 grs. in 200 c.c. sterile distilled water. An initial injection of 20 grs. was given rapidly and the animal became immediately tense, swayed, went down and became comatosed. This was only temporary and there commenced a galloping movement with the limbs, gasping respirations, spasm of eyelids. All muscles were in a great state of tone including the anal sphincter. Following the preliminary injection, the administration was continued and a total of 20 grs. was given within the first minute. The pulse at this stage was 90/min. and respirations 18/min. The pupil was widely dilated and there was some relaxation of the tail. A further 10 grs. were given after two minutes, shivering continued, the pulse and respirations were unchanged, remaining at about 100/min. and 18/min., respectively, until the onset of anæsthesia.

Owing to the fact that a considerable quantity of solution went subcutaneously, the onset of anæsthesia was delayed. A total of 60 grs. were given in six minutes and at 7½ minutes the animal was anæsthetised. There was complete relaxation, especially of the limbs, pupils constricted, pulse 76 and imperceptible; the respirations were markedly depressed, varying between eight and ten per minute, and Cheyne-Stokes in nature; there was a characteristic twitching of the nostrils, and the jaw was not moveable. The effect persisted for a period of 19 minutes. The pulse remained weak, at a rate of 76-80/min., respirations 6-8/min., chiefly abdominal in nature. After 16 minutes slight anal reflex and quivering of the eyelids; the limbs remained perfectly relaxed.

The long period of anæsthesia can be accounted for by the slow absorption of drug from subcutaneous tissue (c.f. Case No. 2). After 26 minutes recovery commenced, violent twitching and spasm of the limbs occurred, which led into galloping movements very like the condition occurring in the dog during recovery from Nembutal. At this stage the animal was destroyed with i/v. magnesium sulphate in concentrated solution.

Case No. 2: Bay Stallion Pony aged four years, weight approximately 390 lb. calculated from measurements. Normal health. Normal pulse 50/min., temperature 99.9 deg. F., resps. 14/min. Anæsthesia: A calculated dose of 1/5 gr. per lb. was dissolved in sterile distilled water, i.e., 80 grs. in 160 c.c. 20 grs. were administered slowly over a period of three minutes; the animal became apprehensive, tense, excited and paddled with feet. Pulse rose to 100/min. and respirations to 20/min. The animal was allowed to go down, where it lay trembling, tense, with galloping movements of limbs, dilated nostrils and dilated pupil. A further 15 grs. were given slowly; the trembling quickly ceased and relaxation became apparent, tail reflex disappeared, corneal reflex sluggish. A temporary cessation of respirations occurred, but recommenced without stimulation. A further 10 grs.

were given slowly. Thus within ten minutes a total of 45 grs. had been given which produced complete muscle relaxation of limbs. Respirations were chiefly abdominal in nature, very depressed, the rate varied from 3-5 per minute and were Cheyne-Stokes in nature. The pulse remained at 84-90/min. and as anæsthesia persisted dropped to 76/min. Corneal reflex almost disappeared, tail completely relaxed.

A satisfactory state of anæsthesia persisted for six minutes after cessation of injection. After which stimulation produced movement of the limbs, trembling, paddling and galloping movements as in Case No. 1. 35 grs. were then given very rapidly in order to assess the degree of toxicity of the drug. Muscle relaxation again became complete, corneal reflex was almost lost, but within five minutes the dose had not proved fatal. The respirations were very depressed varying between one and three per minute. The animal was destroyed with 2 oz. chloral hydrate i/v. In this case anæsthesia had been produced which lasted for a period of six minutes. The dose necessary was 45 grs., i.e., approximately $\frac{1}{8}$ gr. per lb. B.W.

Summary

A brief account is given of the use of "Intraval Sodium" as a short acting anæsthetic in the dog, cat and horse.

The dosage and period of anæsthesia are dependent on the rate of administration.

The characteristics of the drug are the short action, rapid recovery period, depressant action on the respirations and complete muscular relaxation.

There is an absence of narcotic excitement in the dog and cat, but this is not so for the horse.

The anæsthetic properties are briefly compared with those of "Pentothal Sodium" and "Nembutal."

Acknowledgments

I would like to record my thanks to Professor C. Formston for the interest he has taken in making these observations, and to Lt.-Col. J. Hickman, M.R.C.V.S., and Mr. J. Greatorex, M.R.C.V.S., for their help and co-operation.

THE EPIDEMIOLOGY OF TUBERCULOSIS*

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THE earliest observation on the contagious nature of tuberculosis occurs in the Ordinances of Manu in India, thirteen centuries B.C. In these, pulmonary consumption and swelling of the glands of the neck are declared to be unclean, incurable diseases. Those who wanted to marry are cautioned not to select a

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spouse from a consumptive family even though the family had a good lineage and possessed great wealth. These laws show a knowledge of tuberculosis, and as the disease was regarded as an impediment to marriage it seems likely that it was regarded as contagious. In Europe the earliest reference to the contagious nature of tuberculosis was made by the Greek orator Isocrates in his *Aegineticus* (§ 29), written about 390 B.C. In this he states: "The majority of those who had nursed this disease [phthisis] had themselves fallen victims to it." The Hippocratic school, however, did not generally subscribe to this view, preferring the idea of the tuberculosis diathesis which has persisted even to the present day. About one hundred years later Aristotle realised that consumption could be spread by close contact with the diseased person. Galen and Avicenna held similar views. It is more than a tragedy that these early Greek observations were disregarded and forgotten in later centuries, for it was only towards the end of the seventeenth century that in Latin countries such as Spain and Italy the contagious nature of the disease was again being recognised. In Britain, Edward Mainwaring was possibly the first to assert that tuberculosis was spread by contact, as in 1667 he wrote: "You must not frequently converse with a phthisical person whose unwholesome breath may infect the sound by drawing in putrid vapours which the other breathes forth, but above all a phthisical bedfellow is most dangerous to affect a sound person and chiefly to be avoided."

Later, in 1694, Richard Morton in his book *Phthisiologia,* which is an outstanding presentation of the symptomatology of tuberculosis, wrote: "A contagious principle also propagates the disease, for, as I have found by experience, an affected person may poison a bedfellow by a kind of miasm like that of a malignant fever." Towards the middle of the nineteenth century, however, leaders of the profession like Bright and Addison (1839), also Graves (1843), almost completely disregarded the contagiousness of tuberculosis, and attached great importance to diathesis. This unparalleled reverence for the past with its diathesis had so dominated men's minds that little or no progress had been made for centuries regarding the true nature of the disease. Laennec (1826), though he unified the whole concept of tuberculosis by asserting that wherever tubercles occurred the disease was tuberculosis, was of the opinion that at least in France tuberculosis was not usually contagious. That tuberculosis could be produced in animals by inoculation with tuberculous material was shown in 1843 by Klencke, and in 1868 Villemin finally proved experimentally that tuberculosis was an infectious disease. It was Villemin who first showed that tuberculous material from bovine sources was more virulent for rabbits than that from human. In 1867 William Budd, of North Tawton, as a result of a study of the geographical distribution of consumption in past and present times, concluded: "The tuberculous matter itself is (or includes) the specific matter of the disease and constitutes the material by which phthisis is propagated from one person to another and disseminated throughout society." Even after the discovery of the tubercle bacillus by Koch in 1882 we find from the Collective Investigation Record (British Medical Association, 1883) that many British physicians reported that they had never observed a case of probable transmission of the disease from a case of phthisis. Later, Theobald Smith (1896, 1898) reported the existence of "a distinctively human or sputum, and a bovine variety of tubercle bacillus."

XUM

Though Koch proved that the tubercle bacillus was the *causa peccans* and stressed the importance of inhalation of infected sputum in the spread of the disease, it is strange how in 1901, while accepting that human and bovine types were different, he yet concluded that the latter was rarely pathogenic for man. Koch (1882) had undoubtedly found the bovine bacillus in human disease, for he had obtained from a case of caseous pneumonia (No. 27) a culture of tubercle bacilli which after inoculation into the anterior chamber of the eye proved virulent for rabbits. In 1911 the British Royal Commission proved conclusively that the bovine bacillus was a definite cause of tuberculosis in man. It is not surprising that Koch went astray when we consider the relative rarity of primary abdominal tuberculosis in Germany as compared with this country. Indeed, Koch himself in his address gave *post-mortem* statistics from various German sources to support the rarity of this condition. At a later date Ghon and Kudlich (1930) found in 2,114 cases of tuberculosis in children in Central Europe a primary intestinal infection in only 24 (1.14 per cent.) and tonsils infection in two (0.09 per cent.).

Cycle of Infection in Human and Bovine Tuberculosis

The two chief varieties of tubercle bacilli to be considered are the human and the bovine types, as they are almost solely responsible for disease in man and in animals. The avian may be dismissed, owing to the rarity of this type of infection in the human subject (Gloyne, 1933; Feldman, 1938; Bradbury and Young, 1946). The human type passes from man to man, more often by droplet infection than through the agency of dried sputum.

Infection with the bovine type is found chiefly in cattle, though many other types of animals and also man are liable to be infected. The chief mode of spread in cattle is by droplet infection, and thus, as in man, the primary lesion is most often in the lungs. Man is infected with bovine bacilli chiefly through the ingestion of contaminated milk, though air-borne infection is also possible, as is well exemplified in the cases of bovine conjunctival tuberculosis in milkers reported by Jensen *et al.* (1940). The cycle of infection, however, does not stop there (Fig. 1), as it has been observed that bovine infection may pass back from man to cattle (Magnusson, 1941, 1942; Griffith and Munro, 1944; Plum, 1940; Nielsen and Plum, 1939; Tice, 1944), and also from man to man, as in the five proved cases reported by Griffith and Munro (1935), Munro (1939), Jensen *et al.* (1940), and Hedvall (1942).

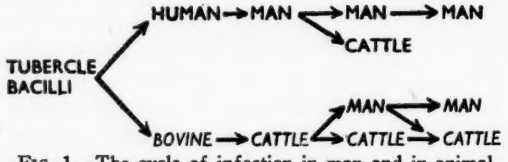

FIG. 1.—The cycle of infection in man and in animal. *British Med. Journal.*

The human type of tubercle bacillus may also infect cattle, as it has been observed that cows in contact with a human case of pulmonary tuberculosis, though developing no sign of active disease, may give positive tuberculin reactions. Many of these cases have been proved by the isolation of a human type of bacillus from the tissues of cattle which may show no active disease or minimal lesions in either the respiratory or the alimentary system (Giltner, 1923; Hindersson, 1933; Stenius,

1933; Bang and Jepsen, 1936; Crawford, M. [personal communication], 1936; Plum, 1937; Van der Schaaf and Van Zweiten, 1939; Reid, 1939; Plum, 1940; Nielson and Plum, 1939; Feldman and Moses, 1941; Hillermark, 1942; Rosa, 1942; Magnusson, 1942). Neither Hindersson (1933) nor Plum (1936, 1937) succeeded in isolating human tubercle bacilli from the milk of cows naturally or experimentally infected with the human type. Thus infection of cattle with the human type is more of a nuisance, as it results in confusion at tuberculin-testing: bovine infection, on the other hand, usually gives rise to serious losses. Someone in contact with a previously clean herd should be suspected when many positive reactors suddenly appear at routine tuberculin-testing.

The cycle of infection in man and in animals is thus much more complicated than originally suspected.

A. INFECTION WITH THE HUMAN TYPE OF BACILLUS

1. Respiratory

The chief pathway of infection for tuberculosis in the human subject is via the respiratory system. In a consecutive *post-mortem* series of 434 cases of tuberculosis in children under 13 years the primary site of infection was found in the respiratory system in 283 (65.2 per cent.), in the abdomen in 140 (32.3 per cent.), and in the cervical glands in nine (2.07 per cent.); no definite primary portal of infection could be identified in seven. (In five of the cases there appeared to be double sites of entry—one in the thorax and the other in the abdomen.)

Respiratory tuberculosis is most commonly caused by the inhalation of infected droplets; occasionally, however, pulmonary tuberculosis may be secondary to tuberculosis elsewhere, as, for example, in the mesenteric or cervical glands, due usually to blood spread from these sites. Tubercle bacilli must, however, be frequently inhaled without producing any recognisable lesion, and it must be assumed that in these cases the tubercle bacilli are destroyed by the resistance of the tissues of the healthy individual. It is thus not the bacillus itself, the presence of which is essential, but the harmonious working together of many factors which results in disease. These factors probably play a more important part in the pathogenesis of the disease than the organism, but the true nature of many of them and their mode of action is still obscure. Tuberculosis is a universal disease and the chances of infection are enormous, and it is a native or acquired resistance, or both, which prevents the disease assuming epidemic proportions. Is this resistance humoral or cellular? It would appear to be more associated with the latter, as Lurie (1942) has shown experimentally that tubercle bacilli phagocytosed by the mononuclear leucocytes of normal animals are not killed, whereas the same cells in actively tuberculous or immune animals have increased bacteriostatic or bactericidal properties which seem to be independent of the body fluids, as these properties remain after the cells have been transferred into a normal animal.

In a series of cases of primary respiratory tuberculosis in children under 13 years we isolated the human type of bacillus from the primary lung lesion or the tracheobronchial glands in 160 (96.4 per cent.) and the bovine in six (Table I).

TABLE I.—*Primary Respiratory Tuberculosis; Types of Tubercle Bacilli*

Type	0-1 years	1-2 years	2-3 years	3-6 years	6-13 years	Total
Human	58	31	21	24	26	160 (96.4%)
Bovine	*1*	*2*	*2*	*1*	—	*6 (3.6%)*

Griffith and Munro (1944), in figures collected from various authors, found that the types of tubercle bacilli occurring in the sputum of Scottish patients with pulmonary tuberculosis comprised 2,609 (94.3 per cent.) human and 160 bovine strains, and from cases in England, Wales, and Eire, 4,113 (98.1 per cent.) human and 81 bovine.

In most cases of human infection in childhood the source of infection is usually a near relative, and in a recent series of cases of meningitis of all ages due to the human type of bacillus investigated in Scotland, the mother was the most frequent source (Table II). The significance of this familial infection is

TABLE II.—*Relationship of Contact to* 144 *Cases of Meningitis Infected with Human Strains*

Mother	44	Brother	20	Grandmother	2
Father	22	Aunt	12	Grandfather	6
Sister	21	Uncle	6	Others	11

important, as it subjects those coming in contact with it to repeated infections, and also to the liability of massive doses of tubercle bacilli. Both these factors may overcome any natural or acquired resistance possessed by a member of a family, more particularly should this resistance be lowered by acute disease, overwork, or malnutrition.

In childhood the primary infection results in the primary lung lesion, originally described by Parrot (1876) though often credited to Ghon (1916). It may also occur in adults, and during the war period we observed typical childhood acute primary pulmonary lesions more often in the adult than formerly, due, I think, to the greater number of rural dwellers coming to work in factories in urban areas. The primary lung lesion in the child is usually small and may be readily missed unless carefully searched for at necropsy (Blacklock, 1932). It is usually single, but why this should be so in view of the probability of multiple infections—as, for example, in the case of a child with a tuberculous parent—is unknown. The secondary lesion in the tracheo-bronchial glands in the child under three years is usually massive. The reason for the greater size of the lesion in the glands as compared with that in the lungs would appear to depend on the degree of hypersensitivity which the child has developed in the interval elapsing between the occurrence of the lesion in the lung and that in the glands. Owing to this hypersensitivity the lesion in the glands is more of an exudative type, and thus massive caseation occurs. In the older child the degree of tuberculosis in the tracheo-bronchial glands is usually less than that in the younger; in fact, in older children and adults the glandular lesion may be entirely absent. Terplan (1946) has also noted this. In *post-mortem* examinations in adults small healed primary lung lesions are often found, and in a series of cases still being studied in the Royal Infirmary, Glasgow, only about five per cent. show any evidence of tuberculosis in the tracheo-bronchial glands. This relative absence of secondary lesions in the

glands of older children may be partly accounted for by the more frequent evidence of healing as judged by the growth of fibrous tissue around the primary lung lesion. This fibrosis increases *pari passu* with age (Table III), and will close

TABLE III.—*Primary Lung Foci in Children: Evidence of Healing*

Age	No. of Foci	Percentage Healing
0- 6 months	40 ...	0
6-12 „	58 ...	10.3
1- 2 years	62 ...	37.1
2- 3 „	40 ...	40.0
3- 6 „	44 ...	52.2
6-13 „	46 ...	67.4

lymphatic channels and thus prevent the spread of the bacilli to the glands. This, however, is not the primary reason, for it is obvious that in order to allow granulation tissue to form and subsequent fibrosis to occur the bacilli must be fixed at the site of infection and prevented from undue multiplication, at least for a time, by some bodily defensive mechanism.

Age is undoubtedly an important factor in determining healing. The longer the primary infection in the child is delayed the greater chance of resolution, particularly in the period between five and puberty, but why this should be so is unknown. This probably accounts for the higher mortality in children of the hospital class as compared with those who are better off. In the former there are more opportunities of infection occurring in early life, due largely to the overcrowded conditions under which most of them live, than in the latter, in whom primary infection is usually delayed until school age or later. A further and an important factor is that between five and 14 years there is a greater proportion of changes from a positive to a negative tuberculin reaction than at any other age (Zacks and Sartwell, 1942).

If the disease is not localised at or near the site of infection then, in the child, generalisation occurs, resulting in acute generalised miliary tuberculosis with or without meningitis. The total human percentage for the latter in Scotland was 82.8 as reported by various workers between 1907 and 1947 (Watt, 1907; Wang, 1916-17; Blacklock, 1932; Griffith, 1934; Blacklock and Griffin, 1935; Macgregor *et al.*, 1935; Macgregor and Green, 1937; Munro and Scott, 1936; National Investigation [Scotland], 1943-4). The proportion of human infections was higher in the older than in the young age groups (Table IV). The main portal of entry

TABLE IV.—*Types of Tubercle Bacilli: Cerebral Tuberculosis: Scotland*

Date	0-5 years H.	0-5 years *B.*	6-15 years H.	6-15 years *B.*	Over 15 years H.	Over 15 years *B.*	Total H.	Total *B.*
1907-37 ...	178	*72*	71	*19*	30	*6*	281*	*99**
1943-4 ...	193	*42*	153	*15*	152	*5*	498	*62*
Total ...	371	*114*	224	*34*	182	*11*	779	*161*
Human % ...	76.5		86.8		94.3		82.8	

* Includes two cases, ages not stated.

of human strains is via the lungs, and thus most of these cerebral deaths should be included with tuberculosis of the respiratory system, though by the Registrar-General they are tabulated separately under the heading of "meningeal tuberculosis."

The first infection in the lungs with tubercle is pathologically distinct from all others in that it affects a virgin soil and at its onset is localised. In most cases, particularly in older children and in adults, this localisation persists and complete healing results. But the patient has now developed hypersensitivity, the degree of which varies from patient to patient for some years after the initial infection, though it tends to lessen as age advances. For example, in a series of still unpublished Mantoux tests which Griffin and I made in 1932-4 in 1,732 clinically non-tuberculous children, all under 13 years, testing each child first with 0.1 mg. and thereafter, if negative, with 1 mg. and 10 mg. of old tuberculin, we found that of those who did not react to 0.1 mg. the percentage who gave positive reactions with 1 mg. increased as age advanced. The same was true of those who reacted negatively to 1 mg. but positively to 10 mg. (Fig. 2). On account of this waning hypersensitivity in the older as compared with the younger child there is more of a formative response on the part of the fixed tissues, with resulting localisation of the infection. The tissue reaction to reinfection tuberculosis, which in the adult is usually exogenous, depends on many factors such as degree of hypersensitivity and of immunity, dose and virulence of the infecting bacilli. Of these various factors hypersensitivity is the most easily investigated in the human subject; the others are difficult. Experimentally infected animals in which hypersensitivity has waned have acquired a high degree of resistance to any subsequent infection (Willis, 1928). The same would appear to be the case in the human subject, for in most adults healed primary lesions, often minute, are found *post-mortem*. It should be noted, however, that this acquired resistance is by no means absolute and may be broken down by acute and chronic disease, overwork, and malnutrition. A high degree of hypersensitivity is an unfavourable factor as demonstrated in animals by Rich and McCordock (1929) and in tissue cultures by Rich and Lewis (1928). These authors have shown that tubercle bacilli *per se* cause little necrosis in normal tissue, though they quickly do so when hypersensitivity is present.

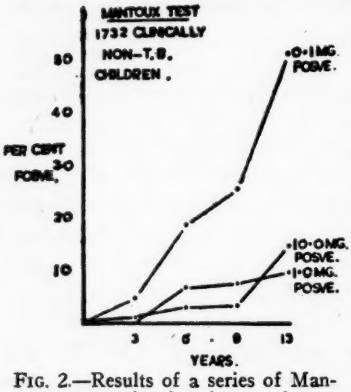

FIG. 2.—Results of a series of Mantoux tests, showing increased percentage of reactions as age advances. *British Med. Journal.*

2. Alimentary Infections

Figures for primary abdominal tuberculosis are small. The collected figures from 1914 to 1944 for Scotland (Mitchell, 1914b; Wang, 1916-17; Blacklock, 1932; National Investigation, 1943-4) show a total percentage of human infections of 22.1 (Table V). As most of the abdominal cases were examined *post-mortem*,

TABLE V.—*Types of Tubercle Bacilli: Tuberculosis of Abdomen and of Cervical Glands: Scotland*

Site and Date	0-5 years H.	0-5 years *B.*	6-15 years H.	6-15 years *B.*	Over 15 years H.	Over 15 years *B.*	Total H.	Total *B.*
Abdomen:								
1914-32 ...	10	*51*	3	*10*	2	*2*	15	*63*
1943-4 ...	3	*5*	1	*2*	2*	*4*	6	*11*
Total ...	13	*56*	4	*12*	4	*6*	21	*74*
Bovine % ...	*81.2*		*75.0*		*60.0*		*77.9*	
Cervical glands:								
1914-35 ...	9	*50*	13	*44*	5	*2*	29*	*102**
1943-4 ...	17	*30*	8	*55*	27	*23*	52	*108*
Total ...	26	*80*	21	*99*	32	*25*	81	*210*
Bovine % ...	*75.5*		*82.5*		*43.9*		*72.2*	

* Two human and six bovine cases included; ages not stated, but under 12 years.

care was taken to exclude any source of infection in the lungs from which the abdomen could have been infected. To account for these primary alimentary lesions human tubercle bacilli must have been swallowed in food contaminated by droplet infection or, in the case of young children, by fingers contaminated from floors on which droplets of sputum may have been present. In the case of children between nine months and 2½ years, Dieudonné (1901) recovered tubercle bacilli from the dirt on their hands in two of 15 cases. Still another method is through the imperfect cleansing of eating utensils, as has been demonstrated by Hutchinson (1947) for dysentery bacilli, streptococci, and staphylococci.

Of the cases of primary tuberculosis of the cervical glands investigated up to 1944 in Scotland (Mitchell, 1914a, 1914b; Griffith, 1915, 1929; Wang, 1916-17; Blacklock, 1932; Griffith and Smith, 1935; National Investigation, 1943-4), the proportion of infections with the human type was 27.8 per cent. The human type of bacillus is thus not mainly responsible for tuberculosis of the abdomen and cervical glands.

B. INFECTION WITH THE BOVINE TYPE OF BACILLUS

1. Alimentary

Infection with the bovine type of bacillus is mainly through the alimentary system, and accounts for the greater proportion of cases of cervical gland and abdominal tuberculosis in the various Scottish investigations (Table V). The highest proportion of bovine infections is found in early life, and this is probably due to the greater consumption of milk at that age than at any other. There are thus greater opportunities for infection should the milk contain tubercle bacilli. As the mucosa of the intestine and of the nasopharynx is a less favourable site than the lungs for attack by tubercle bacilli, which grow slowly, some coincidental lesion may probably allow the bacilli to invade these mucosæ. The more frequent occurrence of acute catarrhal conditions in these sites in childhood as compared with adults may provide a *locus minoris resistentiæ* in which tubercle bacilli may gain a foothold. This may partly account for the greater frequency of tuberculosis of the cervical glands and of the abdomen in children than in adults. Further, the possibility of acquired resistance due to an arrested infection in the

lungs may also determine the relative infrequency of alimentary tuberculosis in the adult as compared with the child. This is well exemplified in the case of a phthisical cavity in the adult where, in spite of a sputum containing numerous tubercle bacilli, secondary tuberculous ulcers may not be found in the intestine.

The rural inhabitant is more liable to bovine infection than the urban, as is shown by the greater incidence of bovine infections in cervical adenitis in country (77.8 per cent.) than in urban patients (46.2 per cent.) (Table VI). The figures

TABLE VI.—*Permanent Residence of Patients: 1943-4 Investigation: Scotland*

Site of Disease	Town		Country	
	H.	*B.*	H.	*B.*
Abdomen	3	*6 (66.7%)*	3	*5 (62.5%)*
Cervical glands ...	28	*24 (46.2%)*	24	*84 (77.8%)*
Cerebral*	306	*20 (6.1%)*	191	*42 (18.0%)*

* In one case residence not stated.

for abdominal tuberculosis are too small to be significant for comparative purposes; those for cerebral tuberculosis, however, show a bovine percentage three times higher in rural than in urban cases. More detailed analysis of the figures obtained in the 1943-4 investigation further confirms this higher proportion of bovine infections in rural areas. In tuberculous meningitis eight per cent. were infected with bovine strains in the large burghs and cities of Scotland, as against 15.9 per cent. in the rural areas of the counties; in surgical tuberculosis 20.1 per cent. of the cases in the burghs and cities were caused by bovine infection; in the rural county areas this percentage was more than double—45.4 per cent. Bovine infection is thus more of a rural than an urban problem. This finding is further substantiated by the figures for the western area of Scotland. In this region 56.7 per cent. of the entire population of the country reside, Glasgow accounting for 39.8 per cent. of the population of the area. In 1914 there were in this area 3,219 (77.5 per cent.) of the 4,138 attested herds in Scotland: in Ayrshire, for example, 88.6 per cent. of the dairy herds are attested. This large proportion of attested herds in the western area partly accounts for this region having the lowest bovine percentage of all areas in Scotland in the meningitis series and the second lowest in the surgical series (Table VII). It is not the whole explanation, which is more

TABLE VII.—*Percentage Bovine Infections: Cerebral and Surgical Tuberculosis: Scotland*

Area	Cerebral	Surgical
Eastern	27.3	54.2
North-eastern	26.7	44.1
South-eastern	13.4	43.7
Northern	8.3	24.0
Western	6.1	27.8

apparent when the figures for the western area are analysed. In the meningitis cases Glasgow had a bovine percentage of 2.3, the large burghs in the Clyde Valley area had together 8.2, and the rural areas in the Western Counties 10.9. The corresponding bovine percentages in the surgical cases for these places were 8.8, 13.6, and 44.4, respectively. In Glasgow 95 per cent. of the milk sold for consumption is subjected to some form of heat treatment (45.9 per cent. pasteurised under licence, 49.1 per cent. heat treated, and five per cent. sold as raw milk), and this accounts in part for the very low bovine percentage in the city. In the

large burghs the proportion of milk subject to some form of heat treatment is lower than in Glasgow, while in the rural districts of the western area from which Glasgow draws its milk supply any form of heat treatment is practically non-existent. Thus in Glasgow, partly owing to the extensive heat treatment of milk, the mortality rate for bovine meningitis is less than one-quarter and the morbidity rate in surgical tuberculosis due to bovine infection is one-fifth of those in the rural areas of the western counties from which it draws its milk supply. Ruys (1946) has made similar observations in Amsterdam, where during the war practically all the milk was pasteurised, and where there was a decrease in bovine tuberculosis in children, though no such decrease was observed in the surrounding rural areas.

Another factor in this difference in the incidence of bovine infection in urban and rural inhabitants which must be considered is an immunological one. Infection with the human type of bacillus must be less common in the country than in the towns, and the rural dweller therefore escapes this type of infection; he consequently develops no tuberculo-immunity, and thus is more liable than the town inhabitant to bovine infection. Indeed, it has been suggested that the presence of bovine bacilli in milk may serve as an immunising agent in the human subject. This is, however, a dangerous doctrine, for neither the dose nor the virulence of the bacillus is under control, and tuberculous disease, often fatal, may result. For example, applying the bovine percentage—namely, 11.1—which we obtained in Scotland during 1943-4 for meningitis to the 1,033 meningeal deaths recorded for these years by the Registrar-General (Scotland), it can be computed that 115 of these were due to infection with the bovine bacillus. Similarly applying the bovine percentage of 33.8 for surgical tuberculosis obtained in the same investigation to the 20,433 cases of surgical tuberculosis notified in these years, it is estimated that 6,906 of the cases were caused by the bovine bacillus.

Reinfection tuberculosis due to the bovine bacillus is unusual, as it is not common to find *post-mortem* evidence of fresh infection in cases of tuberculosis of the abdominal or cervical glands when old lesions already exist. This is in marked contrast to the lung, where the finding of a small healed primary focus, usually without glandular involvement and more recent reinfection tuberculosis, is not uncommon. It is worthy of comment, however, that even in healed cervical and abdominal glands viable tubercle bacilli may still be present; indeed, we have ben able to isolate bovine bacilli from calcified abdominal glands. From such an apparently healed focus tubercle bacilli may escape and cause secondary lesions in bones, joints, urogenital system, etc., years after the primary infection in the glands has taken place.

2. Respiratory Infections

Respiratory tuberculosis of bovine origin is rare, accounting for 3.6 per cent. in our necropsy series in children (Table I), and for 5.7 per cent. of cases in Scotland, and 1.9 per cent. in England, Wales and Eire in the collected figures for all ages reported by Griffith and Munro (1944). In our series bovine bacilli were isolated from the primary lung foci or related tracheo-bronchial glands; thus there is little doubt that the infection was of respiratory origin. Infection in these cases was probably derived from open cases of pulmonary tuberculosis due to the bovine bacillus.

Conclusion

The duty of every medical man is first to prevent disease; if that is not possible, to cure; and if that is impossible, to alleviate. How is this dictum to be applied to tuberculosis? As regards prevention—human infection is the more difficult to control as there are so many known and unknown carriers of the disease in our midst. As Osler (1905) remarked: "The germ of tuberculosis is ubiquitous: few reach maturity without infection, none reach old age without a focus somewhere." It is obviously impossible to segregate all those who may spread the disease; but in factory, in workshop, in school, and in college mass radiography together with adequate clinical examination can play an important part in excluding foci of infection, especially among the young susceptible 15-to-25-years age group, in which tuberculosis is the main cause of death. But mass radiography applied indiscriminately to the population at large will achieve little if we cannot admit to hospital all those who are liable to disseminate the disease, both the young incipient and the old chronic case. Little is eventually to be gained in the control of the disease by dismissing from hospital the old chronic to provide a bed for the young case; that will only result in further spread of the disease. All this is a problem for preventive medicine. Higher standards of living, housing, nutrition and recreation must also play their part: these are problems for social medicine. These measures may help to reduce the incidence of the disease but will not completely eradicate it.

Bovine infection is the easier to control, and in this agriculturists and veterinarians have already accomplished much. The ideal, of course, is that all milk for human consumption should come only from attested herds; but this is a long-term policy, and in the meantime some universal form of adequate heat treatment seems to be the only solution, particularly in view of the bulking of our milk supplies. This is no counsel of despair, as it must be emphasised that in addition to tuberculosis there are many other equally important milk-borne diseases which are preventable by heat treatment, even though all milk eventually comes from attested herds.

Prophylactic vaccination with B.C.G. is still a controversial question, and over 20 years of trial has left the medical profession in a state of confusion as regards its efficacy. Many reports, chiefly from Scandinavia and more recently from America (Aronson and Palmer, 1946), and the recent Memorandum to the Minister of Health (Tytler, 1946) testify to the advisability and the adequacy of this measure. It is uncertain, however, that in a mixed population such as ours the same results would hold as elsewhere, particularly as tuberculosis is such a prevalent disease with us, and frequent infection must be the lot of us all. The discovery by Petroff *et al.* (1927-8) that B.C.G. could dissociate into avirulent R and virulent S forms raised doubts in the minds of many regarding the use of a living vaccine. No definite case of tuberculosis has, however, yet been proved as resulting from the use of properly prepared B.C.G. vaccine. Vaccines of killed bacilli have been employed with apparent success by Goodwin and Schwentker (1934), Opie *et al.* (1939), and Wells *et al.* (1944). As in all tuberculosis research, it will be long before we can assess and pass a final judgment on the efficacy of B.C.G. vaccination. This interval must be at least 15 to 25 years in order to allow us to judge its efficacy in the young adult age group, in which at present

tuberculosis is such a serious problem. Meanwhile, B.C.G. may serve a useful function until chemotherapeutic or immunological research provides us with something as reliable for the cure of tuberculosis as penicillin has been for pyogenic infections. In his Memorandum Tytler (1946) has given all the essentials for a scheme of prophylactic vaccination. It is hoped that those in authority will carefully consider his suggestions, as the disaster at Lübeck is still fresh in our minds.

With regard to the cure of established tuberculous disease, nothing can be added to the valuable contribution which D'Arcy Hart (1946) has made to the chemotherapy of tuberculosis. Streptomycin is still under trial as a curative agent and the results of these trials are awaited with interest.

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NOTICE

THE Iodine Educational Bureau, Stone House, Bishopsgate, E.C.2, have issued booklets, "Iodine On the Farm," "A Guide to First Aid in Animal Husbandry," and "The Place of Iodine in Animal Nutrition." These are now available and the Bureau will be glad to send copies to our readers upon request and without charge.

ANNOUNCEMENT

ONTARIO VETERINARY COLLEGE: AN INVITATION

SIR,—I have the pleasure to convey, on behalf of the Honourable Thomas Kennedy, Minister of Agriculture in the Province of Ontario, the following invitation, transmitted through Mr. J. S. P. Armstrong, Agent General for Ontario, Ontario House, 13, Charles II Street, London, S.W.1 :—

"The Ontario Veterinary College, Guelph, will have an official opening of a new wing on July 1, 1948. It is the wish of Mr. Kennedy and of Dr. McNabb, the Principal, that an invitation be extended to attend this opening to any member of the veterinary profession of the United Kingdom who may be planning to visit Canada in the summer of 1948.

"It would be appreciated if any members wishing to take advantage of this opportunity would write in advance so that suitable arrangements may be made."

Yours faithfully,

D. A. E. CABOT.

Ministry of Agricuture,
99, Gresham Street, London, E.C.2.
August 25, 1947.

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EDITORIAL

ARTIFICIAL INSEMINATION

ARTIFICIAL INSEMINATION, as a means of breeding cattle, is now practised to an increasing extent in this country: the number of centres and sub-centres is gradually extending and in the not distant future there should be a service for all breeders of dairy cattle at least, for those who desire to use it. The Ministry of Agriculture have recently issued an official statement on the extension of artificial insemination in dairy herds for the purpose of increasing the number of calves to be reared for beef purposes. The scheme includes the keeping at centres of beef bulls of breeds which will "colour mark" the calves. It is not intended that this scheme should interfere in any way with the improvement of dairy cattle which is one of the objects of the encouragement of artificial insemination: it is to be confined to the breeding of calves from dairy cows which are unsuited to produce dairy replacements. The breeds of bulls to be used are Hereford, Aberdeen Angus and Galloway, and the service will be free. The scheme came into operation on October 1, and although some time must elapse before it will be in full swing it is hoped to develop on as wide a scale and at as early a date as possible.

With the extension of artificial insemination at the present rate it is essential that still further attention must be given to the health of the semen-producing bulls. There must be no tendency to be any less severe in the tests which are now applied: the health standard which is now demanded in this country must be maintained and, if necessary, raised to a higher level. We read of bulls from the semen of which well over 1,000 cows have been inseminated in a year and the average number of inseminations from groups of bulls appears to be between 500 and 600. It is obvious how much damage could follow the use of semen from bulls capable of transmitting any of the infectious diseases associated with breeding if there was any relaxation in the standard of the examination and testing of the animals. In this connection we draw our readers' attention to the article by Bendixen and Blom which we have pleasure in publishing in this issue of the VETERINARY JOURNAL. It seems clear from the experiences of these observers that we must give more attention to the possibility of bulls being infected by *Br. abortus* and that the tests to be applied for the detection of the infection